CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Osimertinib (Tagrisso) for Non-Small Cell Lung Cancer

January 4, 2019

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

TABLE OF CONTENTS

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by AstraZeneca Canada Inc.** compared osimertinib to gefitinib or afatinib for the treatment of patients with epidermal growth factor receptor (EGFR) mutation positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) that are treatment-naïve and eligible for first-line treatment with an EGFR-TKI.

Table 1. Submitted Economic Model

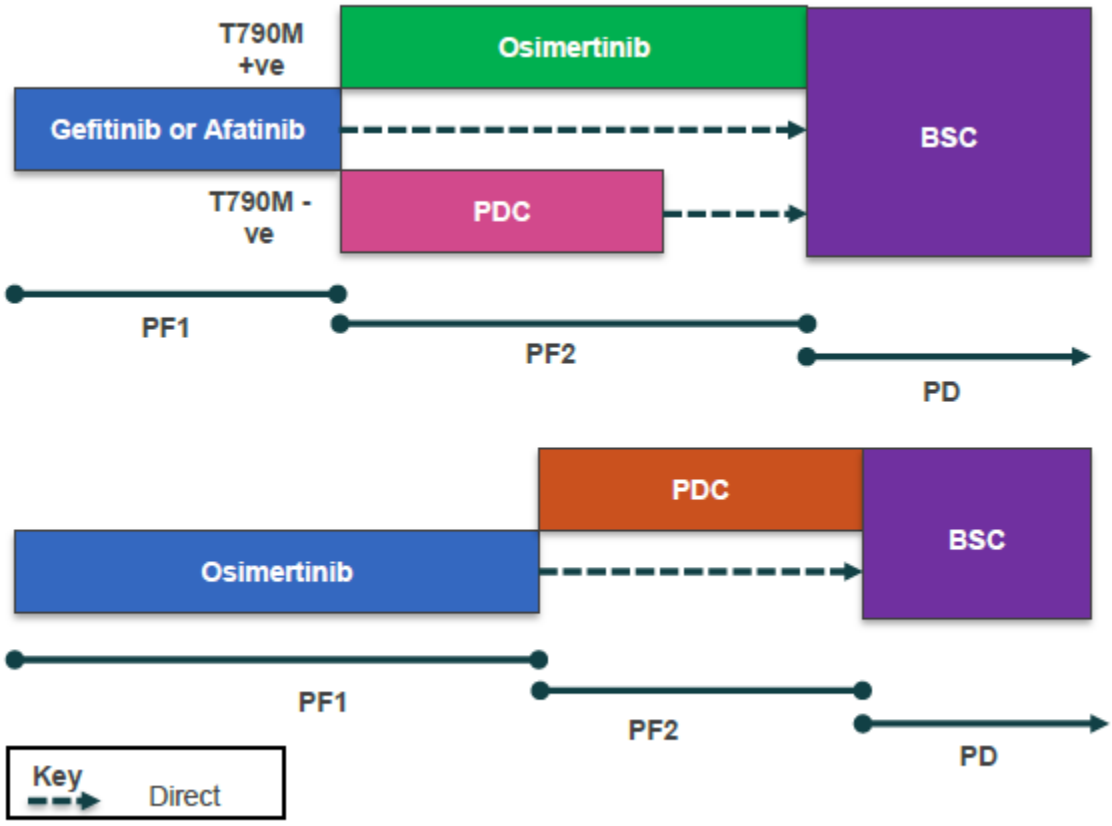
Funding Request	For the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumors have EGFR mutations.
Population modeled	*Patients with EGFR mutation positive, locally advanced or metastatic NSCLC that are treatment naïve and eligible for first-line treatment with an EGFR-TKI*
Type of Analysis	*CUA & CEA*
Type of Model	*Markov*
Comparators	*Gefitinib* *Afatinib* *See* Table 2
Year of costs	*2017*
Time Horizon	*10 years (30-day cycle)*
Discount rate	*1.5% for costs and benefits*
Perspective	*Publicly funded health care payer*
Cost of osimertinib ** Price Source: QuintilesIMS accessed [March 30, 2018]*	Osimeritinib costs $294.68 for the 40mg or 80 mg tablet. At the recommended dose of 80mg once daily, osimeritinib costs • $294.68 per day • $8,250.94 per 28-day course
Cost of erlotinib ** Price Source: QuintilesIMS accessed [March 30, 2018]*	Erlotinib costs $68.00 per 150 mg tablet. At the recommended dose of 150mg once daily, erlotinib costs • $68.00 per day • $1,904.00 per 28-day course
Cost of gefitinib ** Price Source: QuintilesIMS accessed [March 30, 2018]*	Gefitinib costs $73.30 per 250 mg tablet. At the recommended dose of 250mg once daily, gefitinib costs • $73.30 per day • $2,052.40 per 28-day course
Cost of afatinib ** Price Source: QuintilesIMS accessed [March 30, 2018]*	Afatinib costs $73.30 per 250 mg tablet. At the recommended dose of 250mg once daily, afatinib costs • $73.30 per day • $2,052.40 per 28-day course
Model Structure	*Four health states included: progression-free (1st line treatment), progression-free (2nd line treatment), progressed disease and death. All patients start in the first-line progression-free state.* *See* Figure 1
Key Data Sources	*FLAURA – phase III, double-blind, randomized clinical trial (osimertinib vs gefitinib/erlotinib). The submitter assumed that gefitinib and afatinib have equal efficacy in the submitted base case model. Based on this assumption, the FLAURA trial informed the progression-free survival curve and time to progression curve for afatinib.*

	Data for the progressed state came from AURA and IMPRESS for relevant populations. The CGP said these trials were relevant.
**Drug costs for all comparators in this table are based on costing information under license from QuintilesIMS concerning the following information service(s): DeltaPA. and may be different from those used by the submitter in the economic model. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of QuintilesIMS.*	

Table 2. Provincial funding summary of 1st and 2nd line EGFR-TKIs, as taken from pCODR submission

	BC	AB	SK	MB	ON	QC	NB	NS	PEI	NL
Gefitinib	1L	1L	1L	1L	1L	1L	NL	NL	NL	NL
Erlotinib	2L or 3L	1L	1L	2L	2L	2L	2L	1L	2L	2L
Afatinib	1L	1L	1L	1L	1L	1L	1L	1L	1L	1L

Figure 1. Model structure



BSC: best supportive care; PDC: platinum doublet chemotherapy; PD: progressed disease; PF: progression free

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate.

- Relevant issues identified included:
  - *There is net overall clinical benefit from osimertinib as first line therapy in advanced / metastatic NSCLC patients with tumors containing common EGFR mutations. There is substantial improvement in PFS with osimertinib, and data suggests there may be an improvement in overall survival.*
  - *Both osimertinib and standard EGFR TKIs have favourable toxicity profiles in comparison to platinum-based chemotherapy.*
  - *The FLAURA trial allowed treatment beyond progression, and many patients did receive treatment beyond progression.*
  - *Osimertinib is valued highly by clinicians and patients.*

Summary of registered clinician input relevant to the economic analysis
Registered clinician input considered that osimertinib has marked increase in PFS and duration of response to either gefitinib or erlotinib in first line treatment of EGFR mutation positive NSCLC patients with common mutations. Osimertinib is also considered to be r somewhat less toxic (fewer side effects), with similar safety and tolerability to current options. Clinicians stated that osimertinib should be used in the first line setting, prior to platinum doublet chemotherapy, in order to optimize treatment.

Summary of patient input relevant to the economic analysis
Patients with lung cancer are faced with high symptom burden, including fatigue. Patients were also concerned about brain metastasis. Patients who had experience with osimertinib commented on the effectiveness of the treatment and the speed by which patients showed signs of improvement. Patients on osimertinib reported that the symptoms were manageable in light of the improvement in progression-free survival.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG considered the following factors important to consider if implementing a funding recommendation for osimertinib as related to the economic analysis:

- Comparator: The FLAURA trial compared osimertinib to gefitinib and erlotinib, which are funded in some provinces for first line treatment of NSCLC with EGFR mutations. Afatinib is funded in all provinces for first line treatment. The economic analysis assumes equal efficacy between gefitinib and afatinib to inform the economic model.
- Sequencing of osimertinib: PAG sought clarity on whether patients who have started other treatment but have not progressed could switch to osimertinib. The economic model did not consider treatment switching to osimertinib prior to progression. In the economic model, patients continue on their assigned treatment until progression. Upon progression, patients in the gefitinib or afatinib arm could receive osimertinib in the second-line setting, if eligible (based on results of T790M testing).
- Duration of treatment: Treatment duration in the economic model was examined both by the progression-free survival curve and by the time to discontinuation of treatment curve.
- Sequencing following osimertinib: Gefitinib and afatinib are not broadly reimbursed in the second line and beyond. Patients who progress on osimertinib in the economic model were to receive platinum-doublet chemotherapy.

1.3 Submitted and EGP Reanalysis Estimates

Table 3. Submitted and EGP Reanalysis Estimates, gefitinib

Estimates (range/point)	Submitted	EGP Reanalysis Lower Bound	EGP Reanalysis Upper Bound
ΔE (LY)	0.63	0.52	0.44
Progression-free 1	0.75	0.75	0.67
Progression-free 2	-0.13	-0.25	-0.25
Progressed	0.00	0.01	0.01
ΔE (QALY)	0.55	0.47	0.40
Progression-free 1	0.67	0.67	0.61
Progression-free 2	-0.13	-0.22	-0.23
Progressed	0.00	0.01	0.01
ΔC ($)	$145,136	$142,401	$141,598
ICER estimate ($/QALY)	$261,768	$300,460	$354,183

Table 4. Submitted and EGP Reanalysis Estimates, afatinib

Estimates (range/point)	Submitted	EGP Reanalysis Lower Bound	EGP Reanalysis Upper Bound
ΔE (LY)	0.63	0.52	0.44
Progression-free 1	0.75	0.75	0.67
Progression-free 2	-0.13	-0.25	-0.25
Progressed	0.00	0.01	0.01
ΔE (QALY)	0.55	0.44	0.37
Progression-free 1	0.64	0.64	0.58
Progression-free 2	-0.13	-0.22	-0.23
Progressed	0.00	0.00	0.01
ΔC ($)	$141,404	$138,459	$137,686
ICER estimate ($/QALY)	$270,613	$315,639	$370,126

The main assumptions and limitations with the submitted economic evaluation were:

- **Equal efficacy:** Survival estimates for osimertinib were taken from the FLAURA trial, which was a clinical trial examining osimertinib versus gefitinib or erlotinib. There is no head to head trial comparing osimertinib to afatinib. The submitter assumed that gefitinib and afatinib have equal efficacy. Therefore, they did not incorporate an indirect treatment comparison into the economic analysis. Based on the results of the LUX-Lung 7 study and input from the CGP which indicated that there were marginal differences in efficacy between afatinib and erlotinib, this assumption is not unreasonable. Therefore, the gefitinib arm of the FLAURA trial informed progression-free survival and time to progression in the first line setting for the comparison of both gefitinib and afatinib to osimertinib.
- **Treatment duration:** Treatment duration in the first and second line was based on patient level time to progression data. The CGP indicated that patients would most likely stay on osimertinib beyond progression.
- **Proportion of patients receiving 2nd line treatment:** The proportion of patients receiving second line treatment was assumed to be constant over time. In reality this is unlikely to be true. Time to progression (earlier progression versus later progression) and health status will be factors in the decision to provide further treatments. As people who progress

early may be in poorer shape and less likely to receive treatment, an assumption of a constant proportion of receiving 2nd line treatment is not likely to be true.

- Time horizon: The submitted base case time horizon was 10 years. In the initial Economic Guidance Report, the EGP had explored the impact of a 7 year time horizon on the ICER, which increased the ICER by ~$13,000. Following the posting of the initial recommendation feedback from the submitter indicated that a 10 year time horizon is plausible and in alignment with that used in previous pCODR reviews. The EGP and CGP agreed with this rationale and removed the modification to the time horizon for the renalaysis. The EGP, however, reiterated that the economic model is making long-term projections (10-year time horizon) from relatively short follow-up in the FLAURA clinical trial (15 months for osimertinib and 9.7 months for control). Long term extrapolation of survival data with short follow up introduces the risk of overestimating the actual benefit gained with osimertinib.
- Following the posting of the initial recommendation, the submitter commented on the recent (2018) assessment of EQ-5D data from a single institution in Canada (Princess Margaret Hospital). This data related to the quality of life of patients following progression on chemotherapy or an EGFR-TKI. The EGP noted that this study was not made available during the review process and therefore the strengths and weaknesses of the data are unknown. The EGP therefore concluded that it would be inappropriate to comment on any potential impact this information may have on the incremental cost effective ratio.

1.4 Detailed Highlights of the EGP Reanalysis

A. EGP Reanalysis: osimertinib vs gefitinib

The EGP made the following changes to the submitted economic model:

- Time to discontinuation of treatment in the 1st and 2nd line: In the submitted base case, for both lines of treatment (1st and 2nd) time to discontinuation of treatment was determined per the progression free survival curve. The CGP indicated that patients are likely to remain on treatment beyond progression, and to reflect this, the time to discontinuation of treatment curve was chosen instead of the progression-free survival curve.
- Best fitting curves chosen where applicable: In several cases, the best fitting parametric curves were not chosen in the submitted base case. These were for PFS 2nd line osimertinib T790M+ curve, PFS 2nd line PDC curve, TTP 2nd line osimertinib T790M+curve and TTP 2nd line PDC curve. The EGP elected to use the best fitting curves for these inputs in the reanalysis, as no justification was provided by the submitter for the use of alternate curves. Following the posting of the initial recommendation, feedback provided by the submitter noted that pCODR accepted a Weibull curve in a different submission evaluating osimertinib. The EGP noted that one of the sources of data informing the model in the previous review and the current review were both from AURA pooled, in this review, AURA pooled was used to inform PFS and in the previous review it was used to inform OS. It is not known whether the best fitting curve would have been the same as this review. The EGP reiterated that a distribution with the best fit was chosen for the submitted source of data in this review.
- PFS 1st line and TTP 1st line curve: In the submitted base case, there was more than one curve that fit the data appropriately (no parametric curve was ranked number 1 for both AIC and BIC). In order to explore a more conservative fit in the parametric tail for the modeling of PFS 1st and TTP 1st, the EGP explored an alternative best fitting curve.

Table 5. EGP Reanalysis Estimates, gefitinib

Submitter's best case	$145,136	0.55	0.63	$261,768	--
LOWER BOUND					
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from base case
Treatment duration 1st line: time to discontinuation curve	$153,276	0.55	0.62	$278,461	$16,693
Treatment duration 2nd line: time to discontinuation curve	$134,014	0.55	0.63	$242,182	-$19,586
PFS 2nd line osimertinib T790M+: best fitting curve	$138,986	0.52	0.58	$267,688	-$9,295
PFS 2nd line PDC all comers: best fitting curve	$143,297	0.45	0.49	$304,537	$42,769
TTP 2nd line osimertinib T790M+: best fitting curve	$145,783	0.58	0.65	$252,473	-$9,295
TTP 2nd line PDC all comers: best fitting curve	$145,163	0.56	0.63	$260,998	-$770
Best estimate of above 7 parameters	$142,401	0.47	0.52	$300,460	$38,692
UPPER BOUND					
PFS 1st line: alternate best fitting curve, Weibull	$134,868	0.48	0.52	$283,902	$22,134
TTP 1st line: alternate best fitting curve, Weibull	$141,147	0.57	0.65	$255,166	-$6,602
Best estimate of above 9 parameters	$141,598	0.40	0.44	$354,183	$92,415

B. EGP Reanalysis: osimertinib vs afatinib

The EGP made the following changes to the economic model:

- Time to discontinuation of treatment in the 1st and 2nd line: In the submitted base case, for both lines of treatment (1st and 2nd) time to discontinuation of treatment was determined per the progression free survival curve. The CGP indicated that patients are likely to remain on treatment beyond progression, and to reflect this, the time to discontinuation of treatment curve was chosen instead of the progression-free survival curve.
- Best fitting curves chosen where applicable: In several cases, the best fitting parametric curves were not chosen in the submitted base case. These were for PFS 2nd line osimertinib T790M+ curve, PFS 2nd line PDC curve, TTP 2nd line osimertinib T790M+curve and TTP 2nd line PDC curve. The EGP elected to use the best fitting curves for these inputs in the reanalysis, as no justification was provided by the submitter for the use of alternate curves. Following the posting of the initial recommendation, feedback provided by the submitter noted that pCODR accepted a Weibull curve in a different submission evaluating osimertinib. The EGP noted that one of the sources of data informing the model in the previous review and the current review were both from AURA pooled, in this review, AURA pooled was used to inform PFS and in the previous review it was used to inform OS. It is not known whether the best fitting curve would have been the same as this review. The EGP reiterated that a distribution with the best fit was chosen for the submitted source of data in this review.

- PFS 1st line and TTP 1st line curve: In the submitted base case, there was more than one curve that fit the data appropriately (no parametric curve was ranked number 1 for both AIC and BIC). In order to explore a more conservative fit in the parametric tail for the modeling of PFS 1st and TTP 1st, the EGP explored an alternative best fitting curve.

Table 6. EGP Reanalysis Estimates, afatinib

Submitter's best case	$141,404	0.52	0.63	$270,613	--
LOWER BOUND					
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from base case
Treatment duration 1st line: time to discontinuation curve	$149,327	0.52	0.62	$288,345	$17,732
Treatment duration 2nd line: time to discontinuation curve	$130,329	0.52	0.63	$250,442	-$20,171
PFS 2nd line osimertinib T790M+: best fitting curve	$135,365	0.48	0.58	$279,329	$8,716
PFS 2nd line PDC all comers: best fitting curve	$139,611	0.42	0.49	$296,549	$25,936
TTP 2nd line osimertinib T790M+: best fitting curve	$141,991	0.54	0.65	$261,331	-$9,282
TTP 2nd line PDC all comers: best fitting curve	$141,504	0.52	0.63	$269,683	-$930
Best estimate of above 7 parameters	$138,459	0.44	0.52	$315,639	$45,056
UPPER BOUND					
PFS 1st line: alternate best fitting curve, Weibull	$131,252	0.44	0.52	$295,454	$24,841
TTP 1st line: alternate best fitting curve, Weibull	$141,556	0.54	0.65	$263,164	-$7,449
Best estimate of above 9 parameters	$137,686	0.37	0.44	$370,126	$99,513

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include:

- Funding osimertinib in the 2nd line. When the EGP included the option of funding osimertinib in the second line (both reference and new scenario) the 3-year budget impact decreases by 11%.
- Based on feedback from the CGP, the EGP examined increasing the market share of osimertinib in the funded scenario to 70%, 80% and 85% for years 1, 2, and 3, respectively, which substantially increases the 3-year budget impact by 314%.

Key limitations of the BIA model include the use of claims data to estimate the budget impact. Though claims based data may be an appropriate methodology for the province of Ontario, it may not accurately reflect the budget impact in other provinces where complete coverage for oral chemotherapy is provided through government programs. Furthermore, when cost associated with the Canadian population are considered, it is likely that the BIA will increase substantially.

1.6 Conclusions

A. Osimertinib vs gefitinib

The EGP's best estimate of ΔC and ΔE for osimertinib when compared to gefitinib is:

- Between $300,460/QALY and $354,183/QALY.
- The extra cost of osimertinib is between $142,401 and $141,598 (ΔC). *In the submitted base case, the main factors that influence ΔC include the proportion of patients tested as positive for T790M+, the parametric curve chosen for 1st line progression-free survival and modeling treatment duration in the 2nd line using time to discontinuation. The latter two estimates were incorporated into the EGP's best estimate; the proportion of patients tested as positive for T790M+ (42.6%) was deemed reasonable given the base assumption that all patients were being tested and would likely include many ineligible patients.*
- The extra clinical effect of osimertinib is between 0.40 and 0.47 (ΔE). *In the submitted base case, the main factors that influence ΔE include the proportion of patients receiving 2nd line treatment, parametric curve chosen for the 1st line progression-free survival and the parametric curve chosen for 2nd line progression free survival for PDC all comers. The latter two of these estimates were incorporated into the EGP's best estimate; the proportion of patients receiving 2nd line treatment used in the submitted base case was deemed an appropriate input.*

B. Osimertinib vs afatinib

The EGP's best estimate of ΔC and ΔE for osimertinib when compared to afatinib is:

- Between $315,639/QALY and $370,126/QALY
- The extra cost of osimertinib is between $138,459 and $137,686 (ΔC). *In the submitted base case, the main factors that influence ΔC include the proportion of patients tested as positive for T790M+, the parametric curve chosen for 1st line progression-free survival and modeling treatment duration in the 2nd line using time to discontinuation. The latter two estimates were incorporated into the EGP's best estimate; the proportion of patients tested as positive for T790M+ (42.6%) was deemed reasonable given the base assumption that all patients were being tested and would likely include many ineligible patients.*
- The extra clinical effect of osimertinib is between 0.37 and 0.44 (ΔE). *In the submitted base case, the main factors that influence ΔE include the proportion of patients receiving 2nd line treatment, parametric curve chosen for the 1st line progression-free survival and the parametric curve chosen for 2nd line progression free survival for PDC all comers. The latter two of these estimates were incorporated into the EGP's best estimate; the proportion of patients receiving 2nd line treatment used in the submitted base case was deemed an appropriate input.*

Overall conclusions of the submitted model:

- *Any results regarding the comparison to afatinib are reliant on the assumption that there is equal efficacy between gefitinib and afatinib.*

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Lung Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of osimertinib (Tagrisso) for advanced or metastatic non-small cell lung cancer. A full assessment of the clinical evidence of osimertinib (Tagrisso) for advanced or metastatic non-small cell lung cancer is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

REFERENCES

Walker H, Anderson M, Farahati F, Howell D, Librach SL, Husain A, Sussman J, Viola R, Sutradhar R, Barbera L. Resource use and costs of end-of-Life/palliative care: Ontario adult cancer patients dying during 2002 and 2003. J Palliat Care. 2011 Summer;27(2):79-88.